

WHY MORE WOMEN THAN MEN HAVE CHOLESTEROL GALLSTONES: STUDIES OF BILIARY LIPIDS IN PREGNANCY

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Gallstone research, one of my principal research interests, is especially appropriate for this meeting. In 1929, Rolleston and McNee in their textbook on liver disease pointed out that

"... gallstones are rare in warm and tropical countries and are common in cold and damp cities, probably because these conditions tend to induce catarrh of the biliary tract."¹

This can be a trying area of study. Those of you who have had difficulty with reviewers and editors would be sympathetic with the poor soul who first described gallstones 1500 years ago.

"The earliest mention of concretions in the liver occurred in the work of a Greek physician named Trallianus Alexander, who lived and wrote in the fifth century, but whose work was not published until 1548."²

The incidence of cholesterol gallstones is clearly greater in women than in men, as illustrated in Figure 1. The figure shows that the increase is limited to the childbearing years. Why do more women than men have gallstones? The answer seemed clear in 1935.

"Women are more frequent sufferers, the causes being a lax condition of the abdominal walls, visceroptosis, abdominal tumors, tight lacing, sedentary life, constipation, pregnancy, and inflammatory pelvic conditions."³

The cause is less clear today, but there is increasingly firm evidence that ovarian hormones play a critical role. Some evidence for their importance is described below.

In a Swedish community hospital to which all patients from the community were admitted, the number of cases of cholelithiasis in boys and girls before puberty, although small, was equal, but at puberty there was a sharp increase in cases among girls.⁴ Good epidemiologic studies

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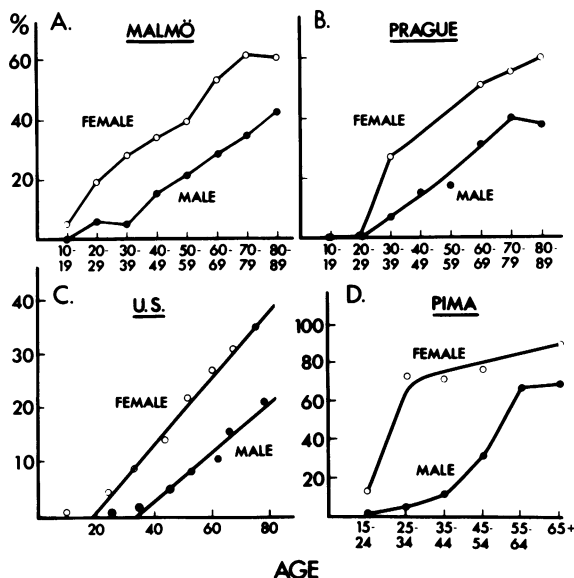


FIG. 1. Incidence of gallstones in four different population groups showing the increase in females during the childbearing years. Reproduced from *Gastroenterology* 75: 512, 1978 with permission.

have shown that the administration of contraceptive steroids to premenopausal women doubles the incidence of gallstones.⁵ The administration of estrogens to postmenopausal women and to men has the same effect.^{6, 7} Bennion and Grundy have recently published a series of studies of biliary lipid composition that help explain some of the sex-related differences. They found that the bile acid pool is smaller in women than in men.⁸ At puberty the bile of girls, but not boys, became more saturated with cholesterol and the bile acid pool sizes, which were equal before puberty, expanded more in boys than in girls.⁹ Both of these changes, increased biliary cholesterol concentration and decreased bile acid pool size, are associated with the formation of cholesterol gallstones.¹⁰ Bennion also studied one young woman before and after bilateral oöphorectomy. The removal of her ovaries was followed by a marked expansion of the size of her bile acid pool and a decrease in the saturation of her bile with cholesterol.¹¹ Further, these investigators found that the administration of contraceptive steroids increased the cholesterol saturation in 9 of 11 women.¹²

Is pregnancy, a physiologic state in which there are very high levels of female sex hormones, associated with an increase in the incidence of gallstones? And if so, what are the biologic mechanisms involved? Clinicians have associated pregnancy with an increase in the risk of gallstones

since the 16th century. Several epidemiologic studies support the association, the best being one by Horn published in 1956¹³ and the Framingham study, published by Friedman and others in 1966.¹⁴ Most early studies of the mechanism focused on gallbladder function. In 1933, Levyn, Beck and Aaron performed cholecystograms on 39 young primiparas in the late stages of pregnancy and found that the gallbladder failed to visualize in 20 of them.¹⁵ In an even more serious violation of today's standards of safety, in 1938 Gerdes and Boyden gave fatty meals to pregnant patients and watched the dye-filled gallbladder empty by means of 12 serial x-rays.¹⁶ They found a marked decrease in rate and extent of gallbladder emptying during the latter half of pregnancy (Fig 2). For obvious reasons there have been no similar recent studies. In one of the first studies of bile composition in pregnant women, Potter in 1936 concluded that "more study and more exact methods are required for better understanding of the bile and gallbladder during pregnancy."¹⁷

We have undertaken an extensive investigation of these problems, and even though the study is far from complete, I shall present some preliminary results. Our general research goals are to determine why more women than men have cholesterol gallstones and whether pregnancy alters biliary lipid composition and secretion in a manner that might contribute to gallstone formation.

We have performed studies in volunteer subjects, about half nonpreg-

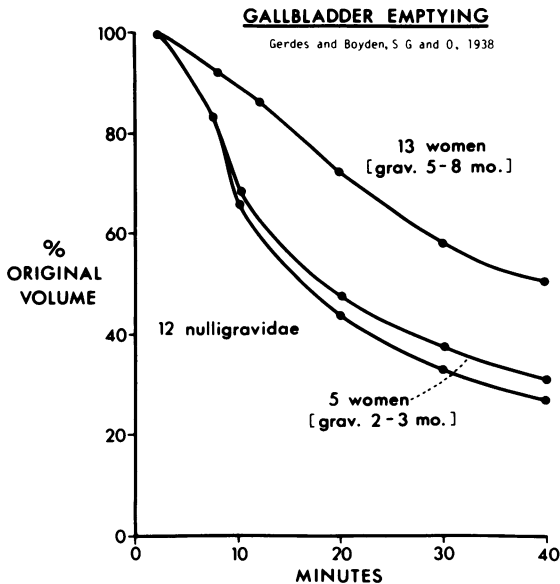


FIG. 2. Gallbladder emptying in response to a standard meal in pregnant and nonpregnant women. Modified from Gerdes and Boyden.¹⁶

nant and the other half in various stages of pregnancy. The mean age of each group was 24. None had symptoms of cholelithiasis and none was obese. They were instructed in a 500 mg cholesterol diet and one week later they were admitted to the Clinical Research Center. A battery of hematologic and biochemical tests showed no difference between the groups except for higher serum lipids in the pregnant subjects. Serum levels of female sex hormones were measured twice by radioimmunoassay during each study period.

A special tube was inserted through the nose into the duodenum, without fluoroscopy in the pregnant subjects, and gallbladder bile was collected after an intraduodenal infusion of amino acids. In some pregnant subjects the biliary lipids contained a higher molar percent cholesterol than most of the non-pregnant subjects. But there was considerable heterogeneity in both pregnant and non-pregnant groups. Although a larger number will have to be studied before clear conclusions can be drawn, the findings to date suggest that pregnancy is associated with a bile that is more saturated with cholesterol.

Gallbladder contractility was assessed in the fasting state by measuring bilirubin output in response to an intraduodenal amino acid infusion for 90 minutes.¹⁸ A nonabsorbable marker was used to permit calculation of bilirubin output. The bilirubin output in our one subject who was kind enough to get pregnant after we had studied her earlier in the non-pregnant state was much less during pregnancy; this suggests that pregnancy may alter gallbladder contractility.

SUMMARY

More women than men have cholesterol gallstones. This is probably to a large extent owing to ovarian hormones. Our preliminary studies suggest that the biliary lipid composition and gallbladder function may be abnormal in pregnancy. Studies are in progress to clarify these suggestive changes. We hope that the studies will allow us to determine the relevance of pregnancy to the pathogenesis of cholesterol gallstones.

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DISCUSSION

DR. CRILEY (Torrance): "I certainly enjoyed your paper and wanted to ask a question about the gallstone prevalence in native Americans or American Indians. Are they cholesterol gallstones and is there a known mechanism for their increased incidence?"

DR. KERN (Denver): "Thank you. Yes, they are cholesterol gallstones. The mechanism of stone formation is known in some. There is a very high incidence of obesity in the Indian population and in obese patients there is an increased secretion of cholesterol. However, the mechanism of gallstone formation is not known in the Indian patients who are not obese. The high incidence of gallstones has been discovered in two groups of Indians—the Pimas in the southwest and the Chippewas in Minnesota. These groups supposedly have different origins and different diets."

DR. BROOKS (Philadelphia): "Fred, do you have any evidence that the effects of obesity and hormones are additive in producing a high incidence of cholesterol gallstones?"

DR. KERN (Denver): "I cannot quote any direct evidence to support that, Frank. I would guess that they were. We have no studies in obese patients."